EDITORIAL

Periventricular heterotopia

Identifying homogeneity among heterogeneity

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Periventricular nodular heterotopia (PNH) is a malformation of cortical development due to failure of migration of neurons from the ventricular zone to the cortex during embryonic development, typically characterized by nodules of ectopic neurons lining the lateral ventricles, which can be identified on brain MRI. Clinical manifestations are heterogeneous and nonspecific, with the main features being focal seizures and variable degrees of cognitive impairment. Thanks to detailed clinical observations and higher-resolution imaging, it has become increasingly clear that PNH represents a clinically and genetically heterogeneous group of disorders.

Advances in the genetics of this syndrome have also clarified our understanding of the syndrome's heterogeneity. The best characterized and most frequently encountered form of PNH is caused by mutations in the *FLNA* gene, encoding the cytoskeletal protein filamin A, inherited in an X-linked dominant pattern.[1] Other forms of PNH in which a genetic defect has been identified include autosomal recessive PNH and microcephaly caused by mutations in *ARFGEF2*[2] and PNH linked to several chromosomal rearrangements.[3–6] In their 2006 review of 182 cases with PNH, Parrini et al.[7] identified 13 subtypes of PNH based on anatomic distribution and associated defects. Ten of 182 patients presented with a distinctive syndrome of bilateral PNH of the temporo-occipital regions and trigones, associated with cerebellar hypoplasia and hippocampal malformation. Typical cases of X-linked PNH due to *FLNA* mutation are characterized by nodules of neurons on the surface of the lateral ventricles, without the specific distribution and additional malformation observed in these patients, so it was not surprising that *FLNA* mutation analysis was negative in 7/7 of these cases, suggesting that additional genetic associations are yet to be identified.

In this issue of *Neurology*®, Pisano et al.[8] provide a detailed description of an extended cohort of 50 patients with this specific syndrome. The main clinical features include epilepsy, cerebellar signs, and mild to moderate cognitive impairment, as well as autistic features in a minority of patients. The majority presented during childhood. All cases were sporadic except for an affected mother and son. MRI in all patients showed multiple bilateral gray matter nodules predominantly adjacent to the trigones and the occipital and temporal horns, and under-rotated and rounded hippocampi. Other associated MRI features consisted of cerebellar abnormalities, thinning or agenesis of the corpus callosum, and polymicrogyria. *FLNA* mutation analysis was negative in all 27 cases examined. Microscopic examination of the brain of an affected 20-week-old fetus showed cytoarchitectonic abnormalities of the white matter and cortex overlying the heterotopic nodules, as well as of the cerebellar cortex and dentate nucleus. The characteristic MRI features and absence of *FLNA* mutations suggest that this syndrome does indeed represent a distinct entity. The detailed clinical-radiologic description provided by the authors should facilitate early recognition of this syndrome and help establish its prevalence and prognosis. Unfortunately, at this time identification of the disorder does not seem to provide any direct benefit to the affected patients. However, the delineation of a homogeneous clinical entity should facilitate the exploration of its underlying genetic architecture. At the moment, the jury remains out as to whether this syndrome represents a genetically homogeneous disorder, along the lines of *FLNA*-related PNH, or rather a heterogeneous entity. Next-generation sequencing of the DNA of patients with this particular syndrome may lead to the identification of the underlying gene mutations. Although animal models of PNH have been described,[9,10] the use of novel techniques such as induced pluripotent stem (iPS) cell technology may provide a more reliable model to study the morphologic and functional aspects of this disorder. iPS cells are generated from adult differentiated cells, such as skin fibro-

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blasts, by genetic manipulations that render them similar to embryonic stem cells. They can then be differentiated in culture into many different cell types, including cortical neurons and glia. Studying the neural differentiation of iPS cells from individuals with PNH may reveal abnormalities that can shed light on the pathogenesis of this disorder. Overall, identification of the genetic causes and elucidation of the pathophysiologic mechanisms involved in PNH will improve our understanding of the pathogenesis of this intriguing disorder and will assist genetic counseling in individuals and their families. Better understanding of the underlying neuronal networks and their physiology could lead to better pharmacologic interventions for associated epilepsy.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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